DOCUMENT RESUME

ED 080 139 PS 006 607

AUTHOR	Stern, Evelyn; And Others
TITLE	Sleep State Periodicity in Prematures and Young Infants.
INSTITUTION	California Univ., Los Angeles. Dept. of Pediatrics.
SPONS AGENCY	National Institutes of Health (DHEW), Bethesda, Md.
PUB DATE	[72]
NOTE	22p.; Paper is to be published with revisions in "Developmental Psychobiology"
EDRS PRICE	MF-$0.65 HC-$3.29
DESCRIPTORS	Biology; Child Development; Correlation; *Infants; *Physical Development; *Premature Infants; *Psychological Patterns; *Sleep; Technical Reports
IDENTIFIERS	*Index of Rhythmicity

ABSTRACT

An autocorrelation technique was used to determine the periodicity underlying successive recurrences of specific sleep states (Quiet Sleep and Active Sleep). Groups of short (2-3 hour) polygraphic records and individual all night recordings were analyzed. Active Sleep and Quiet Sleep periodicities at 32 weeks conceptional age were 12 minutes. At 36 weeks, 40 weeks (term), and 1, 3 and 8 months, the periodicity of both Active and Quiet Sleep was consistently in the 40-60 minute range. At all ages, the cycle time of one state was consistently longer than the other. The appearance of clear periodicities underlying both states and the similarity of the periodicities found in 36 week records to those found in much older infants' records indicated that this biological rhythm is basic to human CNS functioning. The Index of Rhythmicity values in these records and other investigators' data suggest that this rhythm reaches a mature form by 36 weeks post-conception. (Author)

SLEEP STATE PERIODICITY

IN PREMATURES AND YOUNG INFANTS

Evelyn Stern
Arthur H. Parmelee
Margaret A. Harris

Department of Pediatrics
University of California at Los Angeles
Los Angeles, Ca., U.S.A.

To be published with revisions in "Developmental Psychobiology"

Address: (A. H. Parmelee) - Department of Pediatrics, UCLA Center for Health Sciences, Los Angeles, Ca., 90024

This research was supported in part by U.S.P.H.S. Grant No. HD-04008. Computing assistance was obtained from the Health Sciences Computing Facility, UCLA, sponsored by NIH Special Research Resources Grant FR-3.

SYNOPSIS

An autocorrelation technique was used to determine the periodicity underlying successive recurrences of specific sleep states (Quiet Sleep and Active Sleep). Groups of short (2-3 hour) polygraphic records and individual all night recordings were analyzed.

Active Sleep and Quiet Sleep periodicities at 32 weeks conceptional age were 12 minutes At 36 weeks, 40 weeks (term), and 1, 3 and 8 months, the periodicity of both Active and Quiet Sleep was consistently in the 40-60 minute range. At all ages, the cycle time of one state was consistently longer than the other.

The appearance of clear periodicities underlying both states and the similarity of the periodicities found in 36 week records to those found in much older infants' records indicated that this biological rhythm is basic to human CNS functioning. The Index of Rhythmicity values in these records and other investigators' data suggest that this rhythm reaches a mature form by 36 weeks postconception.

Key Words: prematures

infants

sleep

periodicity

rhythms

neurophysiology

Along with investigators in every area of the biological sciences, sleep researchers have become increasingly aware of the possibility that regular recurrences of given phenomena may exist and that temporal organization is an important, if not basic, aspect of an organism's behavior. An orderly, cyclic progression of sleep activity has been known for some time and studied in both human infants and adults. Some of the earliest studies of infants focused as much on the temporal organization of sleep behavior as on its behavioral and physiological components (Kleitman and Engelmann 1953; Aserinsky and Kleitman 1955).

Since numerous biological periodicities appear to be endogenous to the organism and sensitive indicators of changes in the surrounding milieu, both external and internal, it is of interest to know how early in the life of the human organism one can find such periodicities. The measurement of variables related to sleep states is of additional interest as an index of neurological integration and CNS functioning.

Differences in fetal activity as a function of gestational age have not been found (Sterman and Hoppenbrouwers 1971). Activity levels and rhythmicity, recorded in utero, were said to be comparable at points as far apart as 21 and 39 weeks conceptional age. But such records are of necessity limited to measurement of motor activity. While the presence or absence of motor activity is a commonly accepted criterion used in discriminating among sleep states, it does not allow for distinguishing between Active Sleep and wakefulness, for example. Polygraphic recording of the prematurely born infant facilitates the ontogenetic assessment of clearly delineated and neurophysiologically meaningful states.

Investigators have differed in their definitions of specific sleep states in infants. However, the problem of defining sleep cycles has proven more perplexing yet. Questions of sequence and the inclusion or exclusion of waking periods have been resolved in a variety of ways, depending on the researcher's biases and goals. The method employed in this study has the advantage of avoiding the need to arbitrarily define a cycle.

METHODS

Polygraphic recordings of respiration, eye movements, body movements and electroencephalographic (EEG) activity were made on a 16 channel Grass Model A electroencephalograph, using previously described techniques (Parmelee, Schulte, Akiyama, Wenner, Schultz and Stern 1968). Two types of recordings were examined: a limited series of all night tracings and an extensive series of shorter recordings.

Short records. A total of 18 normal prematures and 20 full terms constituted the sample, but many of the infants were recorded at more than one age. Prematurely born infants, ranging from 27 to 37 weeks gestational age, were recorded at 32 weeks conceptional age (n = 10), 36 weeks (n = 14), 40 weeks (n = 12) and 3 and 8 months past term (n = 11 at both ages). Full term infants were recorded within the first week of life (n = 16), at 3 months (n = 13) and 8 months (n = 10).

The records were 2-3 hours in length. Respiration pattern, eye movements and body movement were coded separately for each page (20 seconds), which was then classified as Quiet Sleep (QS), Active Sleep (AS), Transitional Sleep (TS), or Awake by computer. If the infant's eyes were open, he was considered to be Awake. For a page to be classified as QS or AS, multiple criteria had to be met simultaneously (QS: regular respiration pattern, absence of eye and body movements; AS: irregular respiration pattern and presence of eye movements). Pages not meeting the criteria for these states were classified as TS. In addition, a minimum duration of 1 minute was required in order for a state to be considered separately from the preceding one; state shifts of shorter duration were ignored and counted as part of the preceding state.

All night records. Four normal full term infants were recorded at various ages: one at 1 week after birth, three at 1 month, one at 3 months, and three at 8 months. The records were between 10.5 and 11.5 hours in duration. All subjects were allowed to fall asleep and awaken spontaneously and were fed on demand.

Pages of these records were visually classified into QS, AS, TS or Awake by the EEG technician, using the same criteria as specified for computer classification. However, since the EEG tracing was readily available for inspection, undoubtedly influencing her judgment, and the criteria were not as rigidly applied as in computer classification, this coding method produced slightly different data than if these tracings had been analyzed in the same way as the short records. A 3 hour segment of one of the all night tracings was analyzed by both methods; a page-by-page comparison yielded 74% agreement, the major difference being that the technician tended to overlook short periods labelled as TS by the computer and considered them to be part of the on-going state.

Data analysis. A simplified autocorrelation method for time series was applied to each record (Globus 1970b). Two computer passes were made on each record. On the first, all QS pages were coded as "1" and all other states as "0" to determine the periodicity of QS. On the second, the AS pages were coded as "1" and the rest as "0". After each sequence of "0"s and "1"s was generated, an autocorrelation was performed. The largest lag was arbitrarily set at 2/3 of the number of pages in the entire record, each lag being a displacement of 20 seconds. The lagged time series was not looped, so that one data point was dropped for each successive lagged series generated.

The number of correspondences between the "0"s and "1"s in the original and the lagged series, after a correction incorporated to account for more "0"s than "1"s, yields a percent agreement figure at each lag. The lag at which the percent agreement is highest represents the periodicity underlying recurrences of the same state. The magnitude of the percent agreement (called the Index of Rhythmicity) indicates the strength of the correspondence between the series. If, as in adults, for example, there is a 90 minute rhythm to successive REM periods, there would be very few correspondences between the original and lagged series at a lag of 45 minutes and the Index of Rhythmicity (IR) would be low. At a 90 minute lag, the IR would be high because almost the total number of possible correspondences would occur. On the other hand, if the recurrence of REM periods were quite variable, the periodicity derived from the data might still be around 90 minutes but the strength of the periodicity, the IR, would be lower.

The IR for the data presented here is the trough-to-peak difference in percent agreement, not the absolute value of percent agreement at the peak.

RESULTS

There were no significant differences between prematurely born and full term infants at 40 weeks conceptional age (term) and 3 and 8 months past term; therefore the data reported for short records at these ages combine the groups.

A general limitation on the results obtained from short records is that, even though coding each 20 second page of a record generated an average of 438 data points per record, this is not really a sufficient number of points to yield highly reliable autocorrelation estimates. Another limitation is that problems encountered in analyzing the short records necessitated discarding a number of records. In some cases, the short record did not contain more than one period of QS or AS, thereby making it impossible to determine periodicity. In a few rare cases, the state did not appear at all in the course of the recording. In some additional cases, the periodicity of QS or AS was difficult to determine with any confidence (Figure 1). The final number of records used is shown in Table I.

The AS and QS periodicities found in all night and short records after 32 weeks conceptional age fall within a relatively narrow time range (Table II). At 32 weeks, both AS and QS periodicities are extremely short. The 4 records for which AS periodicity could be determined at 32 weeks had values of 7, 12, 17 and 78 minutes. A test for extreme values showed 78 to be a significant outlier ($p < .02$), so that only the first three values were considered in calculating the averages (Dixon and Massey 1957).

In general, the figures based on all night records are comparable to those derived from short records. The lesser variability among all night data at 1 and 8 months indicates that these estimates may be more reliable. The most glaring discrepancy between peridocity in all night and short records occurs in QS at 40 weeks. Infant PS's value is considerably shorter than the mean of 63.9 minutes for the group data, and only one short record had a shorter QS cycle time. Without more all night records at this age, it is of course difficult to say whether PS's value is truly at the lower extreme of the range and/or whether the group mean is an over-estimate of the periodicity underlying QS at 40 weeks.

In a further effort to examine the reliability of the periodicity estimates, the 8 all night records were divided into fourths and each quarter treated as if it were a separate record (438 pages in length). The mean periodicities of these "artificial short records" are comparable to those calculated from the group short records and the individual all night records (Table II). Comparisons of the variances of the group short records and the artificial short records showed that there was significantly less variability in data derived from multiple records from the same subjects (Table III). Not surprisingly, then, inter-individual differences appear to be as important a factor as record length in determining variability. When some of the inter-individual variability was controlled by constructing multiple short records from a small number of individuals, the standard deviations were reduced.

At all ages, the periodicity in one state was consistently longer than in the other. At 32 weeks, for 2 out of 3 Ss, QS periodicity was longer than AS; at 36 weeks, QS periodicity was longer in all 4 Ss. At 40 weeks ($n = 14$) and 3 months ($n = 13$), QS periodicity was also more often longer than AS ($p < .05$, Wilcoxon matched-pairs signed-ranks test). But at 8 months, this was reversed and AS periodicity was consistently longer ($n = 14$, $p < .05$, Wilcoxon).

However, there was no correlation at any age between the length of the AS and QS periodicities. Thus at 40 weeks, for example, while an infant's QS cycle time was likely to be longer than his AS cycle time, it was not possible to predict whether the QS to QS interval would be very much longer or only slightly longer than the AS to AS interval.

The IR did not show any maturational trends (Table IV). The higher agreement shown in short records, whether group or artificial, is to be expected because of the manner in which the IR is calculated. The IR was higher in QS for 2 out of 3 Ss at 32 weeks and 3 out of 4 at 36 weeks. At 40 weeks and 3 months, there were no significant differences, but at 8 months, the IR was more frequently greater in AS than in QS ($n = 14$, $p < .01$, Wilcoxon). As with periodicity, there was no correlation at any age between the magnitude of the IR in AS and QS.

DISCUSSION

The periodicities discussed in this paper should not be confused with the length of time a state is maintained. Periodicity refers to the time elapsing between successive recurrences of the same state, which is independent of the duration of an AS or QS period.

As previously noted, a number of short records were eliminated from the final analysis. Two lines of reasoning can be advanced to account for records in which cycling was difficult to evaluate. First, one can hypothesize that there is in fact no periodicity and the indeterminate results in these records reflect the fragmented nature of sleep in the very young infant. This is essentially a maturational hypothesis. At 32 and 36 weeks, AS and QS episodes tend to be short, vary greatly in duration and recur frequently, in contrast to AS or QS episodes at 3 and 8 months, when states are generally sustained for considerably longer periods of time and less frequently interrupted by short periods of other states. However, the data revealed no age-related patterns in the number of records judged difficult to evaluate (Table 1).

Secondly, one can hypothesize that sleep cycling may be more unstable during the first part of the night than later on and that, therefore, short sleep records representing only the early portion of the night can be expected to yield some records in which the periodicity cannot be determined. When the all night records were treated as multiple short records, the number of such records for which AS or QS periodicity was undeterminable was highest in the 1st quarter (37%), lowest in the 2nd quarter (6%) and intermediate in the 3rd and 4th quarters (25%). Thus, instability of sleep during the early part of the night is not a sufficient explanation, since almost as many unusable records were found during the last half of the night. In addition, waking for the late night feeding did not influence the measurability of succeeding portions of the record in any consistent manner, making it appear unlikely that the amount of time elapsing since sleep onset is the determining factor.

The data on hand, unfortunately, do not allow one to clearly reject either line of reasoning. Without more extensive longitudinal data, the possibility cannot be ruled out that cycling may be inherently "weak" or nonexistent in a certain proportion of any sample of very young normal infants, even when recorded all night. On the other hand, lacking evidence of any distinct maturational trends, we feel justified in assuming that the source of inadequate records is their brevity per se, not the organism, so that the results obtained from the remaining short records may be considered to be representative of the periodicities occurring in QS and AS at those age levels.

The considerable statistical variability that plagues investigators dealing with infant neurophysiological data is evident in these data as well. Standard deviations of 10 minutes or greater are common in reports of infants' cycle length, all determined in widely varying ways (e.g., Monod and Pajot 1965; Stern, Parmelee, Akiyama, Schultz and Wenner 1969). However, it must be noted that similarly large standard deviations were reported for intra-individual data based on repeated recordings of adult subjects (Globus 1970b). ¶After reviewing available data from infants, Sterman and Hoppenbrouwers (1971) concluded that cycle duration is variable at all ages but is definitely shorter in the term newborn than in older infants. While agreeing with the first part, the present results contradict the second part of their conclusion. AS periodicity changes very little after 40 weeks and QS periodicity appears to decrease.

What is even more surprising is that sleep state periodicity at as early an age as 36 weeks is very close to that of much older infants. The consistency with which data on cycle lengths, r[illegible]ess of how defined, fall within the 40-60 minute range is striking.

A distinct periodicity is present at all ages, both in QS and in AS. Treating the periodicity of each state separately is not redundant, since the original data were classified into four states. It is possible to conceive of a model in which the recurrence of, say, AS is entirely regular but that of the other states highly unpredictable. That such a model is not correct is shown by the fact that QS periodicity was present at all ages. Similarly, Globus (1970a) has shown that in adults Stages 2 and 3-4, as well as REM, have a clear periodicity. Furthermore, the percent agreement of the IR indicates that the fit between lagged series was comparable in AS and QS. This comparability implies that the stability of the underlying neurophysiological processes is the same in both states.

The marked change in periodicity between 32 and 36 weeks may be attributable to the rapid CNS maturation during this period noted by investigators studying age-related changes in other areas of functioning. Neonatal mortality risk has been calculated to be from two to ten times as great for infants born at 32 weeks gestation as for those born around 36 weeks (van den Berg and Yerushalmy 1966; Behrman, Babson and Lessel 1971; Battaglia and Lubchenco 1967). Notable changes in the auditory evoked response pattern and photic response latencies first appear around 35-37 weeks (Engel 1963; Weitz an and Graziani 1968). Mature respc. .s , a number of neurologic tests were reported to first occur at 36 weeks or during the 32-36 week period (Graziani, Weitzman and Velasco 1968). Changes in certain EEG characteristics, including the appearance of a sleep cycle described as "reminiscent of the adult's", suggested to Dreyfus-Brisac (1966) "a great change in the functioning of the brain at 37 weeks conceptional age. Our interpretation of this phenomenon is that functional interrelations between cortex and reticular formation appear at this period of development Cortical development also becomes important at this period."

Between 32 and 36 weeks the infant undergoes a particularly rapid period of functional and structural CNS development. The very survival of a 32 week premature can be in grave doubt whereas the 36 week premature has already reached a level of maturity similar on many measures to that of the much older infant. From these observations and the present data, the 32-36 week period would appear to be the most fruitful age range for intensive study of human brain maturation.

We have long assumed that sleep states become more stable with maturation. Such characteristics as the simultaneity of various non-EEG measures, the association between EEG patterns and non-EEG parameters, and the length of the given state all increase from the premature period to 8 months past term (Parmelee and Stern 1972). The IRs however showed no systematic change with age and in fact are very close to those reported for adults, in whom the range was 36.2 to 62.6% (Globus 1970b).

This finding, along with the existence of a clear periodicity at all ages and an essentially unchanging periodicity after 32 weeks conceptional age, indicates that the particular biological rhythm under investigation is extremely fundamental, its neurophysiological expression being as fully developed in the otherwise immature organism as in the adult.

REFERENCES

Aserinsky, E. and Kleitman, N. (1955). A motility cycle in sleeping infants as manifested by ocular and gross bodily activity. J. Appl. Physiol., 8:11-18.

Battaglia, F.C. and Lubchenco, L.O. (1967). A practical classification of newborn infants by weight and gestational age. J. Pediatrics, 71:159-163.

Behrman, R.E., Babson, G.S. and Lessel, R. (1971). Fetal and neonatal mortality in white middle class infants. Amer. J. Dis. Child, 121:486-489.

Dixon, W.J. and Massey, F.J. (1957) Introduction to Statistical Analysis. New York: McGraw-Hill Book Co., Inc. P. 276.

Dreyfus-Brisac, C. (1966). The bioelectrical development of the central nervous system during early life. In F. Falkner (Ed.), Human Development. Philadelphia: W.B. Saunders Co. Pp. 286-305.

Engel, R. and Butler, B.V. (1963). Appraisal of conceptual age of newborn infants by electroencephalographic methods. J. Pediat., 63:386-393.

Globus, G.G. (1970a). Rhythmic functions during sleep. International Psychiatry Clinics, 7:15-21.

Globus, G.G. (1970b). Quantification of the REM sleep cycle as a rhythm. Psychophysiology, 7:248-253.

Graziani, L.J., Weitzman, E.D. and Velasco, M.S.A. (1968). Neurologic maturation and auditory evoked responses in low birth weight infants. Pediatrics, 41:483-494.

Kleitman, N. and Engelmann, T.G. (1953). Sleep characteristics of infants. J. Appl. Physiol., 6:269-282.

Monod, N. and Pajot, N. (1965). Le sommeil du nouveau-né et du prématuré. I. Analyse des études polygraphiques (mouvements oculaires, respiration et EEG) chez le nouveau-né à terme. Biol. Neonat., 8:281-307.

Parmelee, A.H., Schulte, F.J., Akiyama, Y., Wenner, W.H., Schultz, M.A. and Stern, E. (1968). Maturation of EEG activity during sleep in premature infants. Electroenceph. clin. Neurophysiol., 24:319-329.

Parmelee, A.H. and Stern, E. (1972). Development of states in infants. In C. Clemente, D. Purpura and F. Mayer (Eds.), Maturation of Brain Mechanisms Related to Sleep Behavior. New York: Academic Press. In press.

Sterman, M.B. and Hoppenbrouwers, T. (1971). The development of sleep-waking and rest-activity patterns from fetus to adult in man. In M. B. Sterman, D.J. McGinty and A.M. Adinolfi (Eds.), Brain Development and Behavior. New York: Academic Press. Pp. 203-228.

Stern, E., Parmelee, A.H., Akiyama, Y., Schultz, M.A. and Wenner, W.H. (1969). Sleep cycle characteristics in infants. Pediatrics, 43:65-70.

van den Berg, B.J. and Yerushalmy, J. (1966). The relationship of the rate of intrauterine growth of infants of low birth weight to mortality, morbidity, and congenital anomalies. J. Pediat., 69:531-545.

Weitzman, E.D. and Graziani, L.J. (1968). Maturation and topography of the auditory evoked response of the prematurely born infant. Develop. Psychobiol., 1:79-89.

TABLE I

NUMBER OF MEASURABLE RECORDS

OUT OF TOTAL NUMBER ANALYZED

	Total Records Analyzed	Records with Measurable AS Periodicity %	n	Records with Measurable QS Periodicity %	n
32 wks.	10	40	4	60	6
36 wks.	14	71	10	28	4
40 wks.-Prematures	12	58	7	58	7
-Full Terms	16	88	14	56	9
3 mons.-Prematures	11	82	9	82	9
-Full Terms	13	62	8	69	9
8 mons.-Prematures	11	73	8	100	11
-Full Terms	10	60	6	90	9

TABLE II

SLEEP STATE PERIODICITY (MINUTES)

		ACTIVE SLEEP			QUIET SLEEP		
		Short Records (Mean)	All Night Records	Artificial Short Records (Mean)	Short Records (Mean)	All Night Records	Artificial Short Records (Mean)
32 wks.		12.0			12.5		
36 wks.		51.3			56.5		
40 wks.		49.3			63.9		
	(PS)		43			39	
1 mon.	(PS)		62	50		60	66
	(HL)		51	56		54	62
	(EM)		42	46		52	40
	Mean		51.7	50.3		55.3	55.1
3 mons.		49.9			60.8		
	(HL)		59			54	
8 mons.		56.3			47.9		
	(PS)		51	47		51	53
	(HL)		50	45		46	45
	(KK)		51	44		48	45
	Mean		50.7	45.7		48.3	47.3

TABLE III

VARIABILITY OF PERIODICITY (MINUTES)

	ACTIVE SLEEP		QUIET SLEEP	
	Short Records (s.d.)	Artificial Short Records (s.d.)	Short Records (s.d.)	Artificial Short Records (s.d.)
32 wks.	5.0		2.7	
36 wks.	23.6		22.9	
40 wks.	16.9		18.1	
1 mon.		8.7		14.0
3 mons.	12.3		14.0	
8 mons.	17.2*	6.0*	14.7**	5.1**

* $F = 8.5$, $df = 13,9$, $p < .01$

** $F = 8.3$, $df = 19,9$, $p < .01$

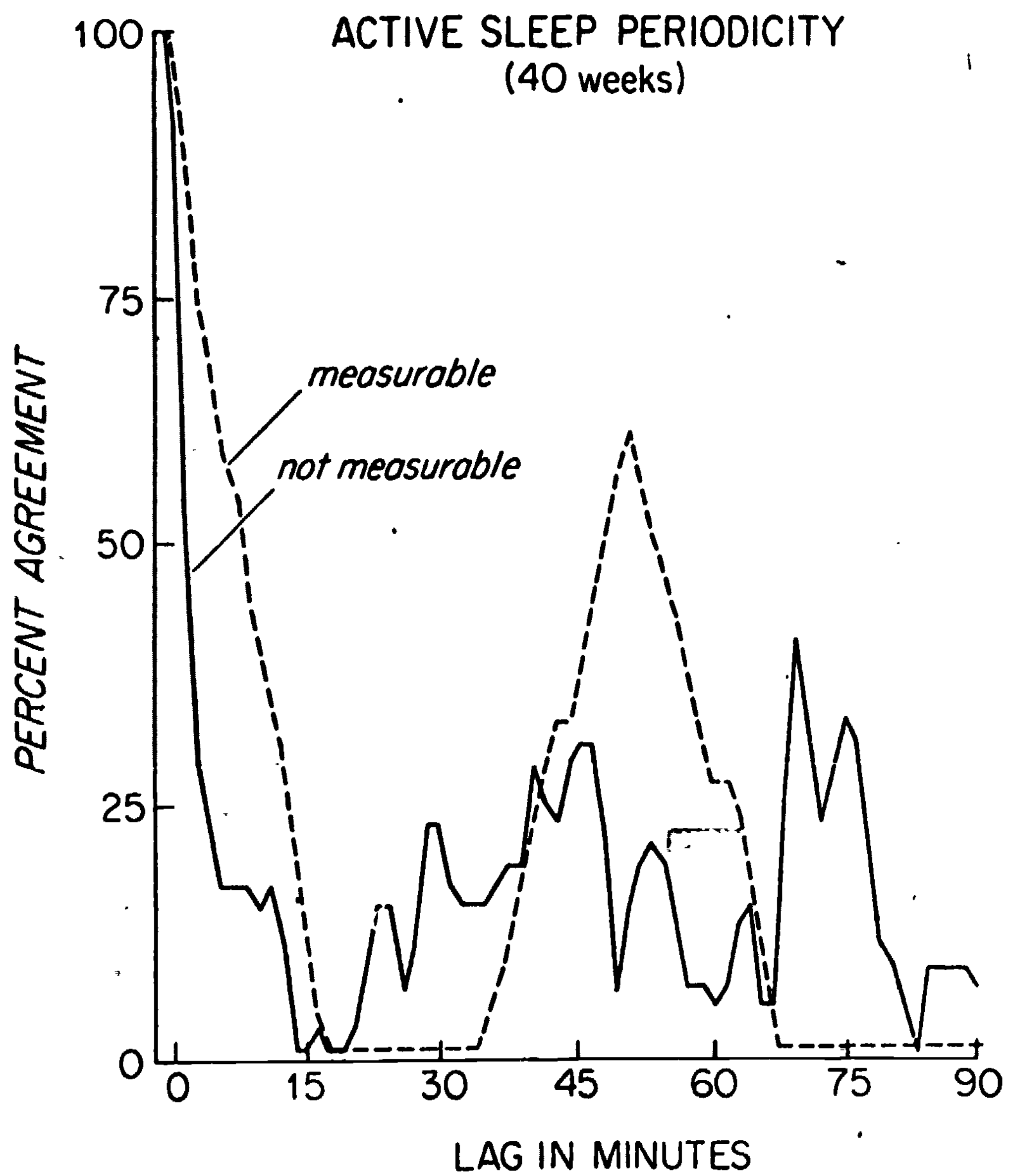
TABLE IV

INDEX OF RHYTHMICITY (% AGREEMENT)

		ACTIVE SLEEP			QUIET SLEEP		
		Short Records (Mean)	All Night Records	Artificial Short Records (Mean)	Short Records (Mean)	All Night Records	Artificial Short Records (Mean)
32 wks.		22.0			37.5		
36 wks.		36.2			36.2		
40 wks.		43.0			54.2		
	(PS)		27			10	
1 mon.	(PS)		21	40		29	68
	(HL)		33	32		25	65
	(EM)		32	53		11	37
	Mean		28.7	42.4		21.7	55.4
3 mons.		41.5			45.5		
	(HL)		50			35	
8 mons.		53.2			29.8		
	(PS)		38	50		35	36
	(HL)		17	23		39	49
	(KK)		17	39		23	42
	Mean		24.0	38.6		32.3	42.9

CAPTION

Figure 1. Plots of autocorrelation results from two infants' records at 40 weeks conceptional age. An AS periodicity, strongest at a lag of 51 minutes, is clearly seen in the "measurable" record. No distinct AS periodicity could be determined in the other record; therefore the data were discarded.


ACTIVE SLEEP PERIODICITY
(40 weeks)
PERCENT AGREEMENT
100
75
50
25
0
measurable
not measurable
0
15
30
45
60
75
90
LAG IN MINUTES